Drug Metabolism and Clinical Response

TOXICITY

EFFICACY

DESIRABLE (therapeutic)

UNDISIRABLE

NON-DELETERIOUS (side effects)

DELETERIOUS (toxic effects)

pharmacological

pathological

genotoxic

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OBJECTIVES

- Understand the fundamental concepts of clinical response
- Describe how the knowledge fundamental concepts of xenobiotic biotransformation aids the rationale use of drugs
- Describe how drug interaction contribute to variability in drug response and drug toxicity
The Relationship between Dose and Effect

Diagram showing the relationship between dose and effect, including:
- Dose of drug administered
- Drug concentration in systemic circulation
- Drug concentration at site of action
- Pharmacologic effect
- Clinical response
- Toxicity and Effectiveness

Pharmacokinetics and Pharmacodynamics:
- Distribution
- Elimination
- Drug in tissues of distribution
- Drug metabolized or excreted

Pharmacological effect may be defined as the **physiological** and/or biochemical changes in the body produced by a drug in therapeutic concentration.

No drug has a single pharmacological effect. A drug usually produces several pharmacological effects.

Pharmacological effects may be classified as **desired** and **undesired** effects even when used in usual dose.

**Undesired effects may be harmless, harmful, or beneficial.** For example, one undesired effect of rifampicin is that it alters the color of urine, feces, sweats and tears to red-orange and this effect is harmless.
PHARMACOLOGICAL EFFECTS

- The concentration of drug in plasma or site of action is seriously taken into account when dealing with drugs having low **therapeutic index** (TI).

- Therapeutic index is the ratio of median toxic dose ($TD_{50}$) to median effective dose ($ED_{50}$).

- So basically **therapeutic index is a measure of the safety of a drug.** The higher the therapeutic index, the higher the safety of that drug and vice versa.

$$ TI = \frac{TD_{50}}{ED_{50}} $$
How do Drugs Exert their Effects?

“That combining group of the protoplasmic molecule to which the introduced group is anchored will hereafter be termed receptor.” PAUL EHRLICH, 1909

Most drugs exert their therapeutic effects by binding to specific receptor sites. Receptors have two important properties - they bind drugs (ligands) with relatively high affinity, and after they bind a drug, they transduce a signal to produce a biological effect.
Types of Target for Drug Action

A. RECEPTORS
- Agonist: Direct action, Ion channel opening/closing, Enzyme activation/inhibition, Ion channel modulation, DNA transcription. Transduction mechanisms.
- Antagonist: No effect, Endogenous mediators blocked.

B. ION CHANNELS
- Blockers: Permeation blocked.
- Modulators: Increased or decreased opening probability.

C. ENZYMES
- Inhibitor: Normal reaction inhibited.
- False substrate: Abnormal metabolite produced.

D. TRANSPORTERS
- Normal transport.
- Inhibitor: Transport blocked.
- False substrate: Abnormal compound accumulated.
RESPONSE TO DRUGS

- Drugs act mainly on cellular targets, producing effects at different functional levels (e.g. biochemical, cellular, physiological and structural).
- The direct effect of the drug on its target produces acute responses at the biochemical, cellular or physiological levels.
- Acute responses generally lead to delayed long-term effects, such as desensitisation or down-regulation of receptors, hypertrophy, atrophy or remodelling of tissues, tolerance, dependence and addiction.
- Long-term delayed responses result from changes in gene expression.
- Therapeutic effects may be based on acute responses (e.g. the use of bronchodilator drugs to treat asthma) or delayed responses (e.g. antidepressants).
ADVERSE DRUG REACTION

WHO – “A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function.”

ADVERSE EVENT

Medical occurrence temporally associated with the use of a medicinal product, but not necessarily causally related.
SIDE EFFECT

- Unintended effect occurring at normal dose related to the pharmacological properties.
- It can also apply to beneficial, but unintended, consequences of the use of a drug.
ADVERSE DRUG REACTIONS

Digestive disturbances—loss of appetite, nausea, a bloating sensation, constipation, and diarrhea—are particularly common adverse drug reactions.

The FDA defines a serious adverse event as one when the patient outcome is one of the following:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability
- Congenital anomaly
- Requires intervention to prevent permanent impairment or damage
Common Side Effects

Nausea
Headache
Stomach pain
Vomiting
Diarrhea
Dizziness
Heartburn
Changes in taste

ADR Symptoms

Alopecia
Headache (AZT, D4T, efavirenz)
Insomnia, depression (efavirenz)
Anemia (AZT)
Cardiomyopathy
Breast hypertrophy
Hepatotoxicity
Nausea, vomiting
Pancreatitis
Nephrolithiasis (indinavir)
Thinning extremities
Central adiposity
Diarrhea
Skin rash
Lactic acidosis
Osteoporosis
Peripheral neuropathy
Ingrown toenails
# Types of ADR

<table>
<thead>
<tr>
<th>Type of ADR</th>
<th>Characteristics</th>
<th>Examples</th>
<th>Management</th>
</tr>
</thead>
</table>
| Type A (augmented) | Dose-related  
Common (overall proportion of ADRs - 80%)  
Suggestive time relationship  
Related to a pharmacological action of the drug  
Predictable from known pharmacology  
Variable severity, but usually mild  
High morbidity  
Low mortality  
Reproducible | *Drug toxicity*  
Nephrotoxicity caused by aminoglycosides  
Dysrhythmia caused by digoxin  
*Side effects*  
Constipation caused by chronic opioid use  
Anticholinergic effects of tricyclic antidepressants  
They derive from:  
*Primary pharmacology* (augmentation of known actions): β-blocker induced bradycardia  
*Secondary pharmacology* (involves different organ or system, but explainable from known pharmacology): β-blocker induced bronchospasm | Reduce dose or withhold  
Consider effects of concomitant therapy |
| Type B (bizarre) | Not dose-related  
Uncommon  
Not related to a pharmacological action of the drug  
Not predictable from known pharmacology  
Variable severity, proportionately more severe than type A  
High morbidity  
High mortality  
Not reproducible | *Intolerance*  
Tinnitus caused by small doses of aspirin  
*Allergy (hypersensitivity or immunological)*  
Result of an immune response to a drug: Penicillin- induced urticaria  
*Pseudoallergic (non-immunological)*  
Immediate, generalised reaction involving mast-cell mediator release: respiratory syndromes caused by NSAIDs  
*Idiosyncratic* (unexpected response to a drug, not related to an allergic mechanism)  
Anticonvulsant hypersensitivity syndrome reaction | Withhold and avoid in the future |
| Type C (chronic) | Uncommon  
Related to cumulative dose  
Long term exposure required | Hypothalamic-pituitary-adrenal axis suppression by corticosteroids | Reduce dose or withhold; withdrawal may have to be prolonged |
| Type D (delayed) | Uncommon  
Usually dose-related  
Seen on prolonged exposure to a drug or exposure at a critical time | Teratogenesis  
Carcinogenesis  
Tardive dyskinesia caused by antipsychotic medication | Often intractable |
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose dependency</td>
<td>Dose Related</td>
<td>Dose Relationship is unclearly defined</td>
</tr>
<tr>
<td>Frequency of Occurrence</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Severity of Reaction</td>
<td>Variable but usually mild</td>
<td>Variable, but proportionately more severe</td>
</tr>
<tr>
<td>Host factors</td>
<td>Genetic factors might be important</td>
<td>Dependent on host factors</td>
</tr>
<tr>
<td>Animal models</td>
<td>Usually reproducible in animals</td>
<td>Unknown in animal models</td>
</tr>
<tr>
<td>Percentage proportion of adverse drug reaction</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Predictable from known pharmacology</td>
<td>Yes</td>
<td>Not usually</td>
</tr>
<tr>
<td>First detection (Clinical Trials)</td>
<td>Phase I - III</td>
<td>Phase IV, occasionally phase III</td>
</tr>
<tr>
<td>Clinical burden</td>
<td>High morbidity &amp; Low Mortality</td>
<td>High morbidity &amp; High mortality</td>
</tr>
</tbody>
</table>
ADVERSE DRUG REACTIONS (อาการไม่พึงประสงค์จากยา)

ปฏิกิริยาที่เกิดขึ้นโดยไม่ตั้งใจ และเป็นอันตรายต่อร่างกายมนุษย์ และเกิดขึ้นเมื่อใช้ยาในขนาดปกติเพื่อการป้องกัน วินิจฉัย บรรเทา หรือป่าวิรัศนากาโรค หรือเพื่อเปลี่ยนแปลงแก้ไขการทำงานของอวัยวะในร่างกายมนุษย์

ADVERSE EVENTS (เหตุการณ์ไม่พึงประสงค์)

อาการทางคลินิกหรือผลทางห้องปฏิบัติการใด ๆ ก็ตามที่เกิดขึ้นที่เราไม่พึงประสงค์ ซึ่งอาจเกิดจาก 1) ความผิดปกติใด ๆ ก็ได้ที่เกิดขึ้นกับคนปกติ 2) disease/complications และ 3) จากสารเคมีหรือยา

SIDE EFFECTS (ผลข้างเคียงของยา)

ปฏิกิริยาที่เกิดขึ้นเนื่องจากฤทธิ์ทางเภสัชวิทยาของยา เกิดขึ้นในขนาดของยาที่ใช้รักษา สามารถคาดการณ์ได้ว่าจะเกิด และระดับความรุนแรงจะขึ้นกับขนาดของยา
Poison is any substance, including any drug, that has the capacity to harm a living organism.

Poisoning can occur in many ways following both therapeutic and nontherapeutic drug or chemical exposure.

The incidence of unintentional, non-iatrogenic poisoning is primarily affecting exploratory young children, ages 1-5 years, and the elderly.

Intentional overdose with pharmaceuticals is most common in adolescence and through adulthood.

83% of human poison exposures reported to the NPDS (AAPCC's National Poison Data System) were unintentional, 13% were intentional and 2.5% were adverse drug reactions.
### Top five agents involved in drug-related death

<table>
<thead>
<tr>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
</tr>
<tr>
<td>Opioids</td>
</tr>
<tr>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
</tbody>
</table>

### Substances most frequently involved in human poisoning exposures

<table>
<thead>
<tr>
<th>Substance</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>12.5</td>
</tr>
<tr>
<td>Personal care products</td>
<td>9.1</td>
</tr>
<tr>
<td>Cleaning substances</td>
<td>8.7</td>
</tr>
<tr>
<td>Sedatives/antipsychotics</td>
<td>6.2</td>
</tr>
<tr>
<td>Foreign bodies</td>
<td>5.1</td>
</tr>
<tr>
<td>Topical preparations</td>
<td>4.5</td>
</tr>
<tr>
<td>Cold and cough medications</td>
<td>4.5</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>4.0</td>
</tr>
</tbody>
</table>
PARACETAMOL - Side effects vs. Toxicity

**Side effects - Rare**
- bloody or black, tarry stools
- bloody or cloudy urine
- fever with or without chills (not present before treatment and not caused by the condition being treated)
- pain in the lower back and/or side
- pinpoint red spots on the skin
- skin rash, hives, or itching
- sore throat (not present before treatment and not caused by the condition being treated)
- sores, ulcers, or white spots on the lips or in the mouth
- sudden decrease in the amount of urine
- unusual bleeding or bruising
- unusual tiredness or weakness
- yellow eyes or skin

**Acute paracetamol poisoning**
- Nausea and vomiting

**Delayed paracetamol poisoning**
- hepatotoxicity
Role of Drug Metabolism in the Safe and Effective Use of Drug

- Any xenobiotics entering the body must be eliminated through metabolism and excretion in the urine or bile/feces.
- In the case of drugs, metabolism normally results in the inactivation of their therapeutic effectiveness and facilitates their elimination.
- The extent of metabolism can determine the efficacy and toxicity of a drug by controlling its biological half-life.
# Role of Drug Metabolism in the Safe and Effective Use of Drug

<table>
<thead>
<tr>
<th>Metabolizer Phenotype</th>
<th>Drug Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard drugs</td>
</tr>
<tr>
<td></td>
<td>Prodrugs*</td>
</tr>
<tr>
<td>Poor Metabolizer (PM)</td>
<td>Reduced elimination</td>
</tr>
<tr>
<td></td>
<td>Increased toxicity risk</td>
</tr>
<tr>
<td></td>
<td>Decreased effectiveness</td>
</tr>
<tr>
<td></td>
<td>Decreased activation</td>
</tr>
<tr>
<td>Intermediate Metabolizer (IM)</td>
<td>Increased drug-to-gene and drug-to-drug interaction risk</td>
</tr>
<tr>
<td></td>
<td>Possible increased toxicity risk</td>
</tr>
<tr>
<td></td>
<td>Increased drug-to-gene and drug-to-drug interaction risk</td>
</tr>
<tr>
<td></td>
<td>Possible reduced effectiveness</td>
</tr>
<tr>
<td>Normal Metabolizer (NM)</td>
<td>Performs according to FDA label specifications</td>
</tr>
<tr>
<td>Rapid or Ultra Rapid Metabolizer (RM, URM)</td>
<td>Reduced effectiveness</td>
</tr>
<tr>
<td></td>
<td>Increased elimination</td>
</tr>
<tr>
<td></td>
<td>Increased toxicity risk</td>
</tr>
<tr>
<td></td>
<td>Increased activation</td>
</tr>
</tbody>
</table>
Drug Metabolism and Variability in Drug Response

- Differences among patients in drug metabolizing enzyme in the intestine and liver are common, are often marked, and are frequently major contributors to differences in drug response, including adverse effects.

- CYP3A is probably the most important of all drug-metabolizing enzymes because it is abundant in both the intestine epithelium and in the liver, where it accounts for nearly 50% of the CYP450s, and because it has the ability to metabolize a multitude of chemically unrelated drugs from almost every drug class.

- Differences in the rate of metabolism of a drug can be due to drug interactions.
Drug interaction may be defined as the pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the 2 agents when given alone.

Drug interactions may result from pharmacokinetic interactions (absorption, distribution, metabolism and excretion) or from pharmacodynamics interactions at drug receptors.

Drug interaction may:
- Increase or decrease the therapeutic effect of the drugs
- Create a new effect
- Increase the incidence of an ADR
**DRUG INTERACTIONS**

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A. Mechanisms of Chemical Interactions

- **PHARMACOKINETIC**
  - biotransformation
  - distribution
  - absorption
  - excretion

- **PHARMACODYNAMIC**
  - non-receptor
  - receptor

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B. Classification of Chemical Interactions

- **ADDITIVE**
  - functional
  - chemical
  - dispositional

- **SYNERGISTIC**
  - 1 + 1 > 2

- **POTENTIATION**
  - 1 + 0 = 2

- **ANTAGONISM**
  - 1 - 1 = 0

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**Absorption**
- Altered gastric emptying and GI motility
- Altered stomach pH
- Chelation or adsorption
- Altered intestinal/hepatic transporters

**Distribution**
- Displacement of protein binding

**Metabolism**
- Enzyme induction ****
- Enzyme inhibition ** **

**Renal excretion**
- Inhibition of drug transporters

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Source: Brunton LL, Chabner BA, Knollmann BC: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition: www.accessmedicine.com
It has been estimated that 56% of drugs that are associated with adverse responses are subjected to metabolism by the xenobiotic metabolizing enzymes, notably the CYPs and UGTs.

Inhibitors of certain CYP450 enzymes can influence the bioavailability of a whole group of drugs metabolized by the same enzyme.

Inducers usually contribute to a loss of effectiveness. As a general principle, drugs that are metabolized more quickly and have a lower bioavailability carry a higher potential risk of interactions.

Environmental chemicals and pollutants are also capable of inducing CYP450 enzymes.
## Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Properties promoting drug interaction</th>
<th>Clinically documented interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>• Chronic alcoholism results in enzyme induction. • Acute alcoholic intoxication tends to inhibit drug metabolism (whether person is alcoholic or not). • Severe alcohol-induced hepatic dysfunction may inhibit ability to metabolize drugs. • Additive central nervous system depression with other central nervous system depressants.</td>
<td><strong>Acetaminophen:</strong> Increased formation of hepatotoxic acetaminophen metabolites (in chronic alcoholics). <strong>Anticoagulants, oral:</strong> Increased hypoprothrombinemic effect with acute alcohol intoxication. <strong>Central nervous system depressants:</strong> Additive or synergistic central nervous system depression. <strong>Insulin:</strong> Acute alcohol intake may increase hypoglycemic effect of insulin (especially in fasting patients).</td>
</tr>
</tbody>
</table>
## DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Properties promoting drug interaction</th>
<th>Clinically documented interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>Inhibits hepatic drug-metabolizing enzymes.</td>
<td><strong>Phenytoin:</strong> Decreased phenytoin metabolism. <strong>Sulfonylurea hypoglycemics:</strong> Decreased sulfonylurea metabolism.</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Metabolism inducible. Enterohepatic circulation of estrogen may be interrupted by alteration in bowel flora (eg, due to antibiotics).</td>
<td><strong>Ampicillin:</strong> Interruption of enterohepatic circulation of estrogen; possible reduction in oral contraceptive efficacy. Some other oral antibiotics may have a similar effect. <strong>Bosentan:</strong> Enzyme induction leading to reduced estrogen effect. <strong>Corticosteroids:</strong> Decreased metabolism of corticosteroids leading to increased corticosteroid effect.</td>
</tr>
</tbody>
</table>
DRUG INTERACTIONS

Drug-drug interaction

Drug-food interaction

Drug-environment interaction
Drug-drug interactions occur when one drug alters the pharmacological effect of another drug.

The pharmacological effect of one or both drugs may be increased or decreased, or a new and unanticipated adverse effect may be produced.

Inhibition of drug metabolism is a frequent cause of drug interactions. Most metabolic interactions are due to competition for the CYP450 enzymes.

Interactions with CYP3A4 are particularly marked, since this isoenzyme has a particularly broad substrate spectrum.
Major mechanisms that increase or decrease enzyme activity

Increase in enzyme activity

**Enzyme inducers**
- enhance gene transcription by activating ligand-activated transcription factors.

**Enzyme activators**
- act directly on enzyme to stimulate its activity.

Decrease in enzyme activity

**Enzyme repressors**
- repress gene transcription by interacting with ligand-activated transcription factors.

**Enzyme inhibitors**
- act directly on enzyme to inhibit its activity.

Transcription → Translation → Enzymes
## Important Perpetrators of CYP450 Drug Interactions

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP1A2</strong></td>
<td>Galangin, furafylline, fluvoxamine</td>
<td><strong>Smoking, charcoal-broiled foods,</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>cruciferous vegetables,</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>lansoprazole, omeprazole</strong></td>
</tr>
<tr>
<td><strong>CYP2C9</strong></td>
<td>Fluconazole, fluvoxamine, sulfaphenazole,</td>
<td><strong>Barbiturates, carbamazepine,</strong></td>
</tr>
<tr>
<td></td>
<td>tienilic acid</td>
<td><strong>rifampin</strong></td>
</tr>
<tr>
<td><strong>CYP2C19</strong></td>
<td>N3-benzynirvanol, fluconazole,</td>
<td><strong>Barbiturates, rifampin</strong></td>
</tr>
<tr>
<td></td>
<td>N3-benzylphenobarbital, nootkatone, ticlopidine</td>
<td></td>
</tr>
<tr>
<td><strong>CYP2D6</strong></td>
<td>Unknown</td>
<td><strong>Bupropion, fluoxetine, paroxetine,</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>quinidine</strong></td>
</tr>
<tr>
<td><strong>CYP3A</strong></td>
<td>Amprenavir, azamulin, boceprevir,</td>
<td><strong>Avasimibe, barbiturates,</strong></td>
</tr>
<tr>
<td></td>
<td>clarithromycin, conivaptan, diltiazem, erythromycin, fluconazole, <em>grapefruit juice</em>, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nefinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, verapamil, voriconazole</td>
<td><strong>carbamazepine, glucocorticoids,</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>pioglitazone, phenytoin, rifampin,</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>St. John's wort</strong></td>
</tr>
</tbody>
</table>
Xenobiotics can influence the extent of drug metabolism by activating transcription and inducing the expression of genes encoding drug-metabolizing enzymes.

Consequences of enzyme induction includes:

- Decrease in pharmacological activity of drugs;
- Increase in activity where the metabolites are active;
- Altered physiological status due to enhanced metabolism of endogenous compounds such as sex hormones.
Some drugs are CYP inducers that can increase not only their own rates of metabolism, but also induce metabolism of other co-administered drugs.

For example, steroid hormones and herbal products such as St. John's wort can increase hepatic levels of CYP3A4, thereby increasing the metabolism of many orally administered drugs.

Indeed, St. John's wort can induce hepatic metabolism of the steroid components of birth control pills, rendering the standard dose ineffective in preventing pregnancy.

Drug metabolism can also be influenced by diet.
Nuclear Receptors that Induce Drug Metabolism

Many ligands and receptors participate in the way to induce drug metabolism. A particular receptor, when activated by a ligand, can induce the transcription of a battery of target genes. Among these target genes are certain drug metabolizing enzyme (CYPs and UGTs) and drug transporters.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aryl hydrocarbon receptor (AHR)</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Constitutive androstane receptor (CAR)</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Pregnane X receptor (PXR)</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Farnesoid X receptor (FXR)</td>
<td>Bile acids</td>
</tr>
<tr>
<td>Vitamin D receptor</td>
<td>Vitamin D</td>
</tr>
<tr>
<td>Peroxisome proliferator activated receptor (PPAR)</td>
<td>Fibrates</td>
</tr>
<tr>
<td>Retinoic acid receptor (RAR)</td>
<td>all-trans-Retinoic acid</td>
</tr>
<tr>
<td>Retinoid X receptor (RXR)</td>
<td>9-cis-Retinoic acid</td>
</tr>
</tbody>
</table>
Induction of Drug Metabolism by Nuclear Receptor–Mediated Signal Transduction
<table>
<thead>
<tr>
<th>Inducer</th>
<th>Major enzymes induced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>CYP3A4, UGT</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>CYP1A2</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>CYP2B6, CYP3A4, UGT</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>CYP2B6, CYP3A4, UGT</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>CYP2B6, CYP3A4, UGT</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>CYP2B6, CYP3A4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NR</th>
<th>Enzymes induced</th>
<th>Examples of inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>AhR</td>
<td>CYP1A1, CYP1A2, CYP1B1, UGT1A1, SULT1A1, GST-A2, ALDH, MDR1</td>
<td>Aryl hydrocarbons, Dioxins</td>
</tr>
<tr>
<td>CAR</td>
<td>CYP2B6, UGT1A1, CYP2C8, CYP2C9, CYP3A4, CYP2A6, SULT1A1, OATPs, MRP3, MRP2</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>PXR</td>
<td>CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1, GST-A2, MDR1, MRP2, OATP2, OCT1</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>GR</td>
<td>CYP3A4, other PXR-induced enzymes</td>
<td>Dexamethasone</td>
</tr>
</tbody>
</table>
CYP450 enzymes may also be induced by substrate stabilization, e.g., decreased degradation, as is the case with:

- troleandomycin- or clotrimazole-mediated induction of CYP3A enzymes,
- the ethanol-mediated induction of CYP2E1, and
- The isosafrole-mediated induction of CYP1A2.
Induction by Inhibition of Protein Degradation

CYP2E1 Formation

CYP2E1 Degradation

Exposure to stabilizer/inhibitor

CYP2E1 Activity

- CYP2E1
- Substrate
- Stabilizer/inhibitor

Time
**ENZYME INDUCTION**

- **Oral contraceptives & steroids**
  - Rifampicin → Induction → CYP3A4 → Inactivated & Excreted → Result → Contraceptive Failure
  - Other CYP3A inducers: Glucocorticoids, Anticonvulsants

- **Paracetamol**
  - Ethanol (chronic) → Induction → CYP2E1 → Toxic Metabolite (N-acetylbenzoiminoquinone) → Result → Hepatotoxicity

- **Non Pharmacological (CYP1A2) inducers**
  - Cigarette smoke → Benzpyrene → CYP1A2 → $\gamma$-Sepoxidation → Carcinogen
  - Activates high dosing requirements of drugs like 'Theophylline' in smokers
  - Polycyclic hydrocarbons, Epoxide formation, Charcoal - barbecued food, Plasticizers (polychlorinated biphenyls)

- **St. Johns Wort**
  - Induction → CYP3A4 → Metabolite → Result → Impaired Immune response, Rejection

- **Cyclosporin**
ENZYME INHIBITION

- It is the phenomenon of decreased drug metabolizing ability of the enzyme by several drugs and chemicals.

- Consequences of inhibition can be:
  - Increase in the plasma concentration of parent drug
  - Reduction in metabolic concentration
  - Exaggerated and prolonged pharmacological effects
  - Increased likelihood of drug-induced toxicity

- Enzyme inhibition is more important clinically than enzyme induction especially for drug with narrow therapeutic index.
ENZYME INHIBITION

Reversible
- Competitive
- Non-competitive
- Uncompetitive

Irreversible
- Irreversible
- Quasi-irreversible
Competitive Inhibition

- It is characterized by competition between substrate and inhibitor for the enzyme’s active site.
- Competitive inhibition occurs when the ‘normal’ substrate and the inhibitor share structural similarities.
- Competition for enzyme binding can be overcome by increasing the concentration of substrate, thereby sustaining the velocity of the enzymatic reaction despite the presence of an inhibitor.
- Examples are included nicardapine (CYP3A4), ketoconazole (CYP3A), celecoxib (CYP2C19), sulfaphenazole (CYP2C9) and quinidine (CYP2D6).
Non-competitive Inhibition

- The inhibitor binds to a separate site on the enzyme, rendering the enzyme–substrate complex nonfunctional.
- Resulting in a decrease of $V_{\text{max}}$ without a change in $K_m$, according to the Michaelis-Menten equation.
- Unlike competitive inhibition, non-competitive inhibition cannot be overcome by increased substrate concentration.
- Examples of pure non-competitive inhibitors are rare but include monoclonal antibodies against CYP450 enzymes and tranylcypromine (CYP2C9; inhibits tolbutamide 4-methyhydroxylation).
Uncompetitive Inhibition

- Uncompetitive inhibition results when the inhibitor binds only to the substrate–enzyme complex.

- It presumes binding of the inhibitor only to the [ES] complex and affects both the $V_{\text{max}}$ and the $K_m$ values, which decrease, but still maintaining the $V_{\text{max}}/K_m$ ratio constant.

- Uncompetitive inhibition of CYP450 enzymes appears rarely, with only one reported instance in which $\alpha$-naphthoflavone inhibited CYP1A2 O-deethylation of phenacetin.
ENZYMES KINETICS

The Lineweaver-Burk plots for inhibition

- **Competitive inhibition**
  - $K_M$ increased
  - $V_{max}$ unaffected

- **Uncompetitive inhibition**
  - $K_M$ reduced
  - $V_{max}$ reduced

- **Noncompetitive inhibition**
  - $K_M$ unaffected
  - $V_{max}$ reduced

Inhibitor lines:
- Blue: no inhibitor
- Red: inhibitor
Irreversible or quasi-irreversible inhibition occurs when either the parent compound or a metabolic intermediate binds to the reduced ferrous heme portion of the CYP450 enzyme, thereby inactivating it.

**Irreversible Inhibition**

In irreversible inhibition, or “suicide inhibition”, the intermediate forms a covalent bond with the CYP protein or its heme component, causing permanent inactivation.

**Quasi-irreversible Inhibition**

In quasi-irreversible inhibition, the intermediate is so tightly bound to the heme portion of the enzyme that it is practically irreversibly bound.
Irreversible Inhibition

- In irreversible inhibition, also referred to as “mechanism-based inhibition” or “time-dependent inhibition”, the time to metabolic recovery is dependent upon the synthesis of new enzyme, rather than upon the dissociation and elimination of the inhibitor, as in the case of reversible inhibition.

- Examples of irreversible inhibitors include the macrolide antibiotics erythromycin and clarithromycin and the HIV protease inhibitors.

- Potent inhibitors of CYP enzymes are typically lipophilic compounds, and often include an N-containing heterocycle, such as a pyridine, imidazole, or triazole functional group.
Reversible (a), Irreversible (b,c) and Quasi-irreversible (d) Inhibition
ENZYME INHIBITION

Types of CYP inhibition

- Reversible interactions, competitive
- Slowly reversible (quasi-irreversible) interactions, non-competitive
- Formation of a reactive intermediate, mechanism-based inhibition

CYP Apoprotein
- Heme prosthetic group
- Iron
- Substrate
- Inhibitor
- Reactive intermediate
- Slowly reversible interaction
- Irreversible interaction

Irreversible (destructive) interactions
Most *in vivo* drug-drug interaction studies compare the plasma drug concentration versus time curve (AUC) of the substrate in the presence and absence of inhibitors.

### Classifications

<table>
<thead>
<tr>
<th>CYP Enzymes</th>
<th>Strong Inhibitors</th>
<th>Moderate inhibitors</th>
<th>Weak inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 5-fold increase in AUC</td>
<td>&gt; 2 but &lt;5-fold increase in AUC</td>
<td>&gt; 1.25 but &lt;2-fold increase in AUC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP Enzymes</th>
<th>Strong Inducers</th>
<th>Moderate Inducers</th>
<th>Weak Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 80% decrease in AUC</td>
<td>50-80% decrease in AUC</td>
<td>20-50% decrease in AUC</td>
</tr>
</tbody>
</table>

Effect of CYP3A4 Induction and Inhibition on Alprazolam
DRUG-FOOD INTERACTIONS

- Some foods and drugs, when taken simultaneously, can alter the body's ability to utilize a particular food or drug, or cause serious side effects.

- A food-drug interaction can:
  - prevent a medicine from working the way it should
  - cause a side effect from a medicine to get worse or better
  - cause a new side effect

- The majority of clinically relevant food-drug interactions are caused by food induced changes in the bioavailability of the drug.
A food–drug interaction is the consequence of a physical, chemical, or physiologic relationship between a drug and a product consumed as food or a nutrient present in a botanically-derived food or dietary supplement.

Food may alter the absorption of oral drugs. In many instances, food slows absorption by slowing gastric emptying time and altering GI secretions and motility.

Food also may decrease absorption by combining with a drug to form an insoluble drug–food complex.
DRUG-FOOD INTERACTIONS

- Biochemical mechanisms include interference with co-factor formation or function, potentiation of drug PD, and modification of drug metabolizing enzyme/transporter function by the dietary substance.

- Grapefruit is the most well-known example, but also sevillian orange, pomelo and star fruit contain agents that inhibit CYP3A4, which is the most important enzyme in drug metabolism.

- Commonly consumed fruit juices, teas and alcoholic drinks contain phytochemicals that inhibit intestinal cytochrome P450 and phase II conjugation enzymes, as well as uptake and efflux transport proteins.
<table>
<thead>
<tr>
<th>Serious adverse event</th>
<th>Drug</th>
<th>Amount of grapefruit consumed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torsade de pointes</td>
<td>Amiodarone&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Juice, 1–1.5 L/d on a regular basis</td>
</tr>
<tr>
<td></td>
<td>Quinine in tonic water&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Juice, high volume during preceding days</td>
</tr>
<tr>
<td>Complete heart block</td>
<td>Verapamil&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Juice, high volume during preceding days</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Atorvastatin&lt;sup&gt;21,22&lt;/sup&gt;</td>
<td>Juice, 1–2 glasses/d for 5 d; juice from fresh grapefruit daily for 2 mo</td>
</tr>
<tr>
<td></td>
<td>Simvastatin&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Whole fruit, 1 fruit/d for 2 wk</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>Tacrolimus&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Marmalade, 1.5 kg eaten during preceding 1 wk</td>
</tr>
<tr>
<td>Myelotoxicity</td>
<td>Colchicine&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Juice, 1 L/d for preceding 2 mo</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>Ethinylestradiol&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Whole fruit, 1 fruit/d for breakfast for preceding 3 d</td>
</tr>
</tbody>
</table>
Grapefruit juice selectively inhibits CYP3A in the enterocyte, with the net result being an increase in the oral bioavailability of felodipine by a factor of three.
# Drug-Food Interactions

<table>
<thead>
<tr>
<th>Food</th>
<th>Drug</th>
<th>What happens?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kale, broccoli</td>
<td><strong>blood thinners</strong> such as warfarin</td>
<td>Foods that are rich in vitamin K can reduce the effectiveness of blood thinners.</td>
</tr>
<tr>
<td>Grapefruit</td>
<td><strong>statins</strong> such as atorvastatin, lovastatin, simvastatin</td>
<td>Grapefruit can increase statin levels in your body, thereby increasing statin-related side effects.</td>
</tr>
<tr>
<td>Bananas (potassium)</td>
<td><strong>ACE inhibitors</strong> such as captopril, enalapril and lisinopril</td>
<td>ACE inhibitors increase potassium in your body. Too much potassium can cause an irregular heartbeat and heart palpitations.</td>
</tr>
<tr>
<td>Walnuts, soybean flour (high fiber)</td>
<td><strong>thyroid medications</strong> such as levothyroxine</td>
<td>High-fiber foods can prevent the body from absorbing thyroid medications.</td>
</tr>
<tr>
<td>Dairy products (calcium)</td>
<td><strong>quinolone antibiotics</strong> such as ciprofloxacin and levofloxacin</td>
<td>Calcium reduces the level of these antibiotics in your blood. Avoid eating dairy and calcium-fortified products alone.</td>
</tr>
<tr>
<td>Salami, aged cheese (tyramine)</td>
<td><strong>oxazolidinone antibiotics</strong> (such as linezolid) and <strong>MAOI-type antidepressants</strong> (such as phenelzine)</td>
<td>Eating a tyramine-rich diet while taking certain meds can cause a sudden, dangerous increase in blood pressure.</td>
</tr>
</tbody>
</table>
## Influence of Food and Drink on Drug Metabolism

<table>
<thead>
<tr>
<th>Diets or status</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-protein / low-carbohydrate diet</td>
<td>CYP1A2 Activity increased</td>
</tr>
<tr>
<td>High-fat diet in rats (olive oil)</td>
<td>Hepatic CYP levels increased</td>
</tr>
<tr>
<td>Low-protein / high-carbohydrate diet</td>
<td>CYP1A2 Activity decreased</td>
</tr>
<tr>
<td>Fat-free diet in rats</td>
<td>Hepatic CYP levels decreased</td>
</tr>
<tr>
<td>High fructose, glucose, sucrose in rats, mice</td>
<td>Hepatic CYP levels decreased</td>
</tr>
<tr>
<td>Fasting or starvation</td>
<td>Complex response (CYP levels and inducibility)</td>
</tr>
</tbody>
</table>
Effects of cruciferous vegetables on xenobiotic metabolism

- Acid condensation products of indoles
- Isothiocyanates

**Procarcinogenic effect**
- AhR Activation
- Inhibition of CYP1A1, CYP2E1
- XRE activation of CYP1A, CYP1B

**Anticarcinogenic effect**
- Nrf2 Activation
- PXR Antagonism
- PXRE upregulation by PXR agonists
- ARE activation of NQO1, EH, UGTs
There are a large number of environmental chemicals that potentially could affect drug biotransformations, usually grouped into heavy metals, industrial pollutants and pesticides.

Exposure to benzo[a]pyrene and other polycyclic aromatic hydrocarbons (PAHs), which are present in tobacco smoke, charcoal-broiled meat, and other organic pyrolysis products, is known to induce CYP1A enzymes.

Other environmental chemicals known to induce CYP450s include the polychlorinated biphenyls (PCBs), which were once used widely in industry as insulating materials and plasticizers, and 2,3,7,8-tetrachlorodibenzop-dioxin (TCDD), a trace byproduct of the chemical synthesis of the defoliant 2,4,5-T.
DRUG-ENVIRONMENT INTERACTIONS

- Nicotine is mainly metabolized in the liver to cotinine by the enzyme CYP2A6.
- Cigarette smoke contains literally thousands of compounds, among which PAHs are primarily responsible for its enzyme-inducing characteristics.
- PAHs have been shown to induce primarily three cytochrome P450 enzymes (e.g., CYP1A1, CYP1A2 and CYP2E1) as well as glucuronosyltransferases.
- Heavy metals regulate CYP1A1 at different levels of its aryl hydrocarbon receptor signaling pathway in a metal- and species-dependent manner.
Induction of CYP1A by Char-Broiled Meat

PAHs (combusted drippings) → AhR Activation → Induction of AhR target genes in the intestinal wall and liver: CYP1A2

AUC of phenacetin [µg ml⁻¹ min]

<table>
<thead>
<tr>
<th>Diet</th>
<th>Home diet</th>
<th>Control: Hamburger, steak in aluminium foil on charcoal, 7 days</th>
<th>Charcoal broiled beef, 4 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 mg Phenacetin p.o.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Phenacetin (7.143) High-extraction drug
# Influence of Pollutants

<table>
<thead>
<tr>
<th>Pollutants</th>
<th>Examples</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organochlorine insecticides</td>
<td>DDT</td>
<td>Induction of CYP3A4, UGT1A1</td>
</tr>
<tr>
<td>Organophosphate insecticides</td>
<td>Parathion</td>
<td>Inhibition of serine esterases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition of CYPs</td>
</tr>
<tr>
<td></td>
<td>Malathion</td>
<td>Inhibition of CYPs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction of CYP1A1, 2C in partridge</td>
</tr>
<tr>
<td>Plasticizers</td>
<td>‘Di-2-ethylhexyl phthalate’ (DEHP)</td>
<td>PXR Agonist, induction of CYP3A4 in vitro</td>
</tr>
<tr>
<td>Combustion products</td>
<td>Benzo[a]pyrene and other PAHs</td>
<td>AhR Agonists, induction of CYP1A1, 1A2, 1B1</td>
</tr>
</tbody>
</table>
# Pathologic Conditions and Drug Response

<table>
<thead>
<tr>
<th>Condition</th>
<th>General effects on drug metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation, infection</td>
<td>Most enzymes: decreased expression and/or activity</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Most enzymes: increased expression</td>
</tr>
<tr>
<td>Liver diseases including tumors</td>
<td>Many enzymes: decreased activity</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Decreased intestinal CYP levels due to impaired mucosa</td>
</tr>
<tr>
<td>Cardiovascular disease with reduced cardiac output; heart failure</td>
<td>Decreased metabolism of high-extraction drugs due to reduced liver blood flow; decreased catalytic activity of some CYPs</td>
</tr>
</tbody>
</table>
EFFECTS OF DISEASE ON DRUG RESPONSE

- Renal excretion of parent drug and metabolites is generally accomplished by glomerular filtration and by specific drug transporters. If a drug or its metabolites are primarily excreted through the kidneys and increased drug levels are associated with adverse effects, drug dosages must be reduced in patients with renal dysfunction to avoid toxicity.

- Even in the absence of kidney disease, renal clearance may be reduced by 35–50% in elderly patients. Elderly patients may display altered drug sensitivity.

- While most drugs used to treat disease in children are the same as those in adults, there are few studies that provide solid data to guide dosing. Drug metabolism pathways mature at different rates after birth, and disease mechanisms may be different in children.
Differences in the rate of metabolism of a drug can be due to drug interactions. Most commonly, this occurs when two drugs are co-administered and are metabolized by the same enzyme.

Metabolism-based drug-drug and other interactions can have significant influence on the use and safety of many drugs.

Induction, by increasing enzyme activity, will result in increased metabolism of certain drugs, contributing to significant inter- and intra-individual variations in drug efficacy and potential toxicity, associated with drug-drug interactions.

The direct consequence of enzyme inhibition is the delay in the biotransformation of certain drugs, resulting thus in increased plasma concentrations and potentiation or prolongation of their pharmacological action.
Elucidation of the mechanisms of specific interactions, especially those related to the enzymes involved in drug metabolism, can and should alert physicians to potential problems if certain drugs are co-administered.

The presence of variant CYP450 alleles and other polymorphisms of drug metabolizing enzyme has important clinical consequences.

In fact, single-gene effects are likely to be less common than effects involving multiple genes, each of which partially contributes to the overall genetic variability in drug response.
The graph illustrates the relationship between plasma concentrations and time, showing:

- **Peak of effect**
- **Duration of action**
- **Therapeutic window**
- **Desired response**
- **Side-effect**
- **Adverse response**
- **Sub-therapeutic**
“5 RIGHTS”

- Right drug
- Right patient
- Right dose
- Right route
- Right time